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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,824	03/14/2002	Gerd Geisslinger	016915-0252	3370

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FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,824	GEISSLINGER ET AL.	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 12-19* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,12-16 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, with traverse, with the Group I, claims 10, 12-16 and 19, is acknowledged. Applicants traverse the restriction requirement on the grounds that both groups of claims share special technical feature since the inhibition of glucuronidase links the invention of group I and II.

This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. Unlike applicant's argument, the instant claims 17-18 do not necessarily require the administration of verapamil or verapamil derivatives. Furthermore, the claims 17-18 further require the co-administration of glucuronide prodrug and glucuronidase bound to a target tissue specific substance. In other words, the administration of verapamil or verapamil derivatives required in Group I invention may not require in Group II invention. The coadministration of glucuronide prodrug and glucuronidase bound to a target tissue specific substance required in Group II may not require in Group I invention. Clearly, the technical feature presented in Group I differs from the Group II invention. Accordingly, Groups I and II are not linked by the same or a corresponding special technical feature as to form a single general inventive concept. Therefore, the requirement is still deemed proper, and made Final. Claims 17-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims, the requirement having been traversed in Response filed March 11, 2004.

Status of Application

2. As indicated in O.A. (page 4, lines 13-14) mailed 06/12/2003, applicant originally has received an action on the merits based on the examiner's interpretation of the claims as "a method of inhibiting human tissue glucuronidase" because applicant filed with improper use claims. However, applicant submitted new claims 10-16 (by an amendment filed 9/12/2003) are directed to an invention, "a method of treating a subject from a condition that is characterized by high human tissue glucuronidase activity" that is independent or distinct from the invention originally claimed invention. Accordingly, applicant's amendment necessitates a new ground of rejection(s) in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 15 is rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly amended claim 15 requires the addition of a glucuronide conjugate of an inflammation-inhibiting active material to the combination of a glucuronidase inhibitor selected from the group consisting of verapamil and verapamil derivatives and a suitable pharmacologically compatible adjuvant, wherein said combination is administered to a subject suffering from a condition that is characterized by high human tissue glucuronidase activity.

The instant specification discloses that the administration of glucuronidase inhibitor reduces the progression and metastasis formation via the inhibition of the tumour glucuronidase (page 2, lines 5-14). The specification also discloses that glucuronidase inhibitor can be sued supportingly in the chemotherapy of cancer patients for the increasing of the desired effect in the case of simultaneous reduction of the undesired actions (page 2, lines 22-26); and glucuronidase inhibitors of the verapamil type can be used supportingly in chemotherapy together with glucuronide prodrug chemotherapeutics (page 6, lines 13-20 and lines 32-34; page 7, lines 3-9).

As discussed above, the specification provides sufficient written description for the two-way combination of glucuronidase inhibitor and a suitable pharmacologically compatible adjuvant or combination of glucuronidase inhibitor and glucuronide prodrug chemotherapeutics. However, the specification clearly do not provide an adequate representation regarding the three-way combination of glucuronidase inhibitor, a suitable pharmacologically compatible adjuvant and a glucuronide conjugate of an inflammation-inhibiting active material made by the presently claimed invention (claim 15). Thus, claim 15 fails to meet the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of the above mentioned glucuronidase inhibitor and a pharmaceutically compatible adjuvant combination or combination of glucuronidase inhibitor and glucuronide prodrug chemotherapeutics, the skilled artisan cannot envision glucuronidase inhibitor, a suitable pharmacologically compatible adjuvant and a glucuronide conjugate of an inflammation-inhibiting active material combination. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

4. Claims 10, 12-14 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Lehnert et al. (British Journal of Cancer, abstract, Apr. 1998, 77(7), pp. 1155-1163).

Lehnert teaches the administration of dexverapamil in combination with epirubicin for the treatment of non-responsive metastatic breast cancer (abstract; "Tumour Response" in pages 1158-1159). Lehnert discloses that toxicity of haemoglobin nadirs was found to be lower in the patients receiving dexverapamil/epirubicin combination compared to epirubicin alone even though other dose-limiting eprubicin toxicities were similar in both treatment groups (page 1157, column 2, 34-48).

Although the reference is silent about whether said condition is characterized by "high human tissue glucuronidase activity" or the functional characteristic of verapamil and verapamil derivatives as "a glucuronidase inhibitor", such property or characteristic is deemed to be inherent to the prior art (Lehnert et al.). It is noted that prior art directing the administration of compounds inherently possessing a therapeutic effect for the same ultimate purpose as disclosed

by Applicants anticipates Applicant's claims even absent explicit recitations of the mechanism of action.

5. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Scheithauer et al. (J Cancer Res Clin Onclo, 1995, 121(Suppl 3), R7-R10).

Scheithauer teaches the administration of dexverapamil, epirubicin and granulocyte/macrophage-colony-stimulating factor for the treatment of advanced or metastatic pancreatic adenocarcinoma (abstract; Discussion).

6. Claims 10, 12-14, 16 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Ratain et al. (US 5786344).

Ratain teaches a method for reducing the toxicity (e.g., diarrhea) of a camptothecin compound (e.g., topotecan, 9-amino-captothecin, 9-nitrocamptothecin, GG 211, irinotecan), comprising administering said camptothecin compound to an animal in combination with dexverapamil (column 2, lines 3-11 and lines 56-67; column 3, lines 1-11; claim 1 and 19).

Although the reference is silent about whether said condition is characterized by "high human tissue glucuronidase activity" or the functional characteristic of verapamil and verapamil derivatives as "a glucuronidase inhibitor", such property or characteristic is deemed to be inherent to the prior art (Ratain). It is noted that prior art directing the administration of compounds inherently possessing a therapeutic effect for the same ultimate purpose as disclosed by Applicants anticipates Applicant's claims even absent explicit recitations of the mechanism of action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jouvin-Marche et al. (Eur. J. Pharmacol., 1983, 89, 19-26).

Jouvin-Marche teaches or suggests that Ca2+ antagonists, namely nifedipine, is useful in inhibiting the secretion of PAF-acether, SRS and beta-glucurinidase in human neutrophils (abstract; page 20, column 1, lines 11-15; TABLE 2; page 24, column 1, lines 14-21 and column

2, lines 5-15). The reference teaches or suggests that deprivation of extracellular Ca2+ by calcium channel antagonists inhibit the secretion of beta-glucurinidase along with PAF-acether and SRS in human neutrophils study (page 24, column 2, lines 10-15). Although the reference mentions verapamil as a Ca2+ antagonist (page 24, line 1 and line 26), the reference does not specifically teach the use of verapamil or its R-enantiomer in inhibiting beta-glucurinidase.

However, one having ordinary skill in the art would have expected that the secretion of beta-glucurinidase is closely related to the extracellular Ca2+ and the inhibition of Ca2+ uptake by Ca2+ antagonists results in inhibition of beta-glucurinidase. It would have been prima facie obvious to the skilled artisan at the time of the invention was made to employ verapamil for inhibiting human tissue beta-glucuridinase since the skilled artisan would have expected that verapamil would have similar activities as nifedipine.

With respect to the use of the R-enantiomers, the individual isomers are obvious variants over the corresponding racemate because of their presence in the racemate. It would further be expected that one of the isomers would be more active than the other, absent evidence to the contrary.

Response to Arguments

7. Applicant's arguments filed September 12, 2003 have been fully considered but they are not persuasive.

Applicant's argument takes position that the person of ordinary skill in the art would have absolutely no expectation that verapamil would inhibit glucuronidase because nifedipine and verapamil are chemically very distinct. Applicant alleges that a person of ordinary skill would immediately comprehend that any common pharmacological property between the two is

conincidental, therefore, in absence of any guiding principle to the contrary, the person would never expect these compounds to necessarily share another but different pharmacological property, inhibition of glucuronidase.

This argument is not persuasive at all. Contrary to the applicant's allegation, the skill artisan would have expected that calcium channel blocker including verapamil would have activity in inhibiting glucuronidase (see Sim et al. "Activation Mechanism of Arachidonic Acid in Human Neutrophil function", abstract, Korean Journal of Pharmacology, 1992, 2891), 91-102; "Mechanism of Organ Failure Following Cardiopulmonary Bypass--Preventive effects of Ca2+ Blocker (Nicardipine)", Hashimoto et al., abstract, Zasshi Journal, Nihon Kyobu Geka Gakkai, 1993, 41, (2), 181-6). Sim teaches or suggests the inhibition of beta-glucuronidase by verapamil. Hashimoto teaches or suggests the inhibition of beta-glucuronidase by nicardipine. Therefore, the skill artisan at the time of the invention was made would have been able to arrive at the claimed invention.

Conclusion

8. The applicant's amendment necessitated a new ground of rejection in this Office Action. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614

ZOHREH FAY
PRIMARY EXAMINER
GROUP 1200